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  *              W E L C O M E   T O   T H E                  *
  *         U. S.   P A T E N T   T E X T   F I L E           *
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=> s adenovirus? and gene therapy and protein IX

          2894 ADENOVIRUS?
         18155 GENE
         37863 THERAPY
          1230 GENE THERAPY
                 (GENE(W)THERAPY)
         62658 PROTEIN
         66033 IX
           243 PROTEIN IX
                 (PROTEIN(W)IX)
L1           8 ADENOVIRUS? AND GENE THERAPY AND PROTEIN IX

=> d l1,1-8,cit,ab


1.  5,780,300, Jul. 14, 1998, Manipulation of non-terminally
differentiated cells using the notch pathway; Spyridon
Artavanis-Tsakonas, et al., 435/377, 325, 366, 372, 375 [IMAGE AVAILABLE]

US PAT NO:      5,780,300 [IMAGE AVAILABLE]            L1: 1 of 8

ABSTRACT:
The present invention is directed to methods for the expansion of
non-terminally differentiated cells ("precursor cells") using agonists of
Notch function, by inhibiting the differentiation of the cells without
inhibiting proliferation (mitotic activity) such that an expanded
population of non-terminally differentiated cells is obtained. The cells
are preferably stem or progenitor cells. These expanded cells can be used
in cell replacement therapy to provide desired cell populations and help
in the regeneration of diseased and/or injured tissues. The expanded cell
populations can also be made recombinant and used for gene
therapy, or can be used to supply functions associated with a
particular precursor cell or its progeny cell.

2.  5,741,772, Apr. 21, 1998, Neurotrophic factor NNT-1; Ming-shi Chang,
514/2; 530/300, 350 [IMAGE AVAILABLE]

US PAT NO:      5,741,772 [IMAGE AVAILABLE]            L1: 2 of 8

ABSTRACT:
Disclosed are nucleic acids encoding novel neurotrophic factors,
designated NNT-1. Also disclosed are amino acid sequences for NNT-1
polypeptides, methods for preparing NNT-1 polypeptides, and other related
aspects.

3.  5,707,618, Jan. 13, 1998, Adenovirus vectors for gene
therapy; Donna Armentano, et al., 424/93.21, 93.2; 435/172.3, 320.1;
514/44 [IMAGE AVAILABLE]

US PAT NO:      5,707,618 [IMAGE AVAILABLE]            L1: 3 of 8
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ABSTRACT:
The present invention relates to novel **adenovirus** vectors for use in **gene therapy** which are designed to prevent the generation of replication-competent **adenovirus** (RCA) during in vitro propagation and clinical use. The invention also provides methods for the production of the novel virus vectors. These vectors maximize safety for clinical applications in which **adenovirus** vectors are used to transfer genes into recipient cells for **gene therapy**.

4. 5,705,151, Jan. 6, 1998, **Gene therapy** for T cell regulation; Steve W. Dow, et al., 424/93.21, 450; 435/7.2, 69.1, 172.3, 320.1; 514/44; 935/54, 55, 62, 71 [IMAGE AVAILABLE]

US PAT NO: 5,705,151 [IMAGE AVAILABLE] L1: 4 of 8

ABSTRACT:
The present invention provides a nucleic acid-based therapeutic composition to treat an animal with disease by controlling the activity of effector cells, including T cells, macrophages, monocytes and/or natural killer cells, in the animal. The present invention also relates to methods of **gene therapy** involving different modes of administration of a therapeutic composition to treat animals with different types of diseases. Also included in the present invention are recombinant molecules for use in a therapeutic composition and recombinant cells useful as a tumor vaccine. Therapeutic compositions of the present invention include superantigen-encoding nucleic acid molecules, either in the presence or absence of a cytokine-encoding nucleic acid molecule, depending upon the disease being treated.

5. 5,670,488, Sep. 23, 1997, **Adenovirus** vector for **gene therapy**; Richard J. Gregory, et al., 514/44; 424/93.2; 435/320.1; 935/62 [IMAGE AVAILABLE]

US PAT NO: 5,670,488 [IMAGE AVAILABLE] L1: 5 of 8

ABSTRACT:
Gene Therapy vectors, which are especially useful for cystic fibrosis, and methods for using the vectors are disclosed.

6. 5,604,201, Feb. 18, 1997, Methods and reagents for inhibiting furin endoprotease; Gary Thomas, et al., 514/12; 435/252.3, 254.2, 320.1; 530/350; 536/23.5 [IMAGE AVAILABLE]

US PAT NO: 5,604,201 [IMAGE AVAILABLE] L1: 6 of 8

ABSTRACT:
This invention relates to methods and reagents for inhibiting furin endoprotease activity and specifically for inhibiting furin endoprotease-mediated maturation of bioactive proteins in vivo and in vitro. The invention specifically provides proteins capable of inhibiting furin endoprotease activity. Particularly provided are .alpha..sub.1 -antitrypsin variants that specifically inhibit furin endoprotease activity. Methods for using furin endoprotease inhibition to attenuate or prevent viral protein maturation, and thereby alleviate viral infections, are provided. Also provided are methods for using furin endoprotease inhibition to attenuate or prevent proteolytic processing of bacterial toxins, thereby alleviating bacterial infections. Methods are also provided to inhibit proteolytic processing of biologically active proteins and peptides. The invention also provides pharmaceutically acceptable compositions of therapeutically effective amounts of furin endoprotease inhibitors.

7. 5,552,529, Sep. 3, 1996, Autoantigen, pinch; Ann Rearden, 530/380; 424/185.1; 530/327, 806, 829 [IMAGE AVAILABLE]

US PAT NO: 5,552, [IMAGE AVAILABLE] 7 of 8

ABSTRACT:
A novel autoantigenic polypeptide, PINCH, polynucleotides and antibodies that bind to PINCH are provided. A method for removing autoantibodies that bind to an epitope contained in PINCH from a sample, such as blood, and a method of treating autoimmune disorders associated with autoantibodies that bind an epitope in PINCH are also provided.

8. 5,534,256, Jul. 9, 1996, Haemophilus somnus outer membrane protein extract enriched with iron-regulated proteins; Andrew A. Potter, et al., 424/184.1, 193.1, 203.1, 236.1, 255.1, 256.1, 278.1, 282.1 [IMAGE AVAILABLE]

US PAT NO: 5,534,256 [IMAGE AVAILABLE] L1: 8 of 8

ABSTRACT:
New subunit vaccines from Haemophilus somnus are disclosed. The vaccines include an outer membrane protein extract of H. somnus which is enriched with iron-regulated proteins. Additional antigens, such as antigens derived from Pasteurella haemolytica, can be included in the vaccine composition to provide protection against a variety of disease states.

=> d 3-5,fro

US PAT NO: 5,707,618 [IMAGE AVAILABLE] L1: 3 of 8
DATE ISSUED: Jan. 13, 1998
TITLE: **Adenovirus** vectors for **gene therapy**
INVENTOR: Donna Armentano, Belmont, MA
Helen Romanczuk, Westboro, MA
Samuel Charles Wadsworth, Shrewsbury, MA
ASSIGNEE: Genzyme Corporation, Framingham, MA (U.S. corp.)
APPL-NO: 08/409,874
DATE FILED: Mar. 24, 1995
INT-CL: [6] A61K 48/00; C12N 15/00; C12N 5/00
US-CL-ISSUED: 424/93.21, 93.2; 435/172.3, 240.1, 240.2, 320.1; 514/44
US-CL-CURRENT: 424/93.21, 93.2; 435/172.3, 320.1; 514/44
SEARCH-FLD: 514/44, 2; 435/235.1, 172.1, 172.3, 240.1, 240.2, 91.1; 424/93.2, 93.21
REF-CITED:

FOREIGN PATENT DOCUMENTS

WO9412649	12/1993	World Intellectual Property Organization
9424297	10/1994	World Intellectual Property Organization
9502697	1/1995	World Intellectual Property Organization
WO9511984	5/1995	World Intellectual Property Organization

OTHER PUBLICATIONS

Zabner et al., Gene Therapy 3:458-465, 1996.
Armentano et al., Human Gene Therapy 6:1343-1353, 1995.
Krougliak et al., Human Gene Therapy 6:1575-1586, 1995.
Welsh et al., Human Gene Therapy 6:205-218, 1995.
Wadsworth et al., J. Cell Biochem. Supp. 21A, Abstract No. c6-450, 1995.
Setoguchi et al., Blood 84:2946-2953, 1994.
Engelhardt et al., Human Gene Therapy 5:1217-1229, 1994.
Armentano et al., J. Cell Biochem. Supp. 18A, Abstract no. DZ 102, 1994.
Wilkinson et al., Nucleic Acids Res. 20:2233-2239, 1992.
Rosenfeld et al., Cell 68:143-155, 1992.
Jolly, D., Cancer Gene Therapy 1:51-64, 1994.

Marshall, Science: 269:1050-1055, 1995.
Neve, Trends in Neuroscience 16(7):251-253, 1993.
Berkner, BioTechniques 6(7):616-629, 1988.
NIH, "Report and Recommendations . . . ", Dec. 7, 1995, pp. 1-40.
Vincent et al., Nature Genetics 5:130-134, 1993.
Descamps et al., Human Gene Therapy 5:979-985, 1994.
Stratford-Perricaudet et al., Human Gene Therapy 1:241-256, 1990.
Mitani et al., Human Gene Therapy 5:941-948, 1994.
Haddada et al., Human Gene Therapy 4:703-711, 1993.
Jaffe et al., Nature Genetics 1:372-378, 1992.
Zabner, J. et al., Nature Genetics 6:75-83, 1994.
Rich, D. et al.,Human Gene Therapy 4:461-476, 1993.
Zabner, J. et al., Cell 75:207-216, 1993.
Crystal, R.G. et al., Nature Genetics 8:42-51, 1994.
Bridge, E. et al., J. Virol. 63:631-638, 1989.
Huang, M. et al., J. Virol. 63:2605-2615, 1989.
Klessig, D. et al., Mol. Cell. Biol. 4:1354-1362, 1984.
Weinberg, D. et al., Proc. Natl. Acad. Sci. USA 80:5383-5386, 1983.
ART-UNIT: 184
PRIM-EXMR: Jacqueline M. Stone
ASST-EXMR: Andrew Milne
LEGAL-REP: Brumbaugh, Graves, Donohue & Raymond

ABSTRACT:
The present invention relates to novel **adenovirus** vectors for use in **gene therapy** which are designed to prevent the generation of replication-competent **adenovirus** (RCA) during in vitro propagation and clinical use. The invention also provides methods for the production of the novel virus vectors. These vectors maximize safety for clinical applications in which **adenovirus** vectors are used to transfer genes into recipient cells for **gene therapy**.
8 Claims, 3 Drawing Figures

US PAT NO: 5,705,151 [IMAGE AVAILABLE] L1: 4 of 8
DATE ISSUED: Jan. 6, 1998
TITLE: **Gene therapy** for T cell regulation
INVENTOR: Steve W. Dow, Denver, CO
Robyn E. Elmslie, Denver, CO
ASSIGNEE: National Jewish Center for Immunology & Respiratory Medicine, Denver, CO (U.S. corp.)
APPL-NO: 08/446,918
DATE FILED: May 18, 1995
INT-CL: [6] A61K 48/00; C12N 15/63; C12N 15/09; C12N 5/00
US-CL-ISSUED: 424/93.21, 450; 514/44; 435/69.1, 172.3, 7.2, 320.1; 935/62, 55, 54, 71
US-CL-CURRENT: 424/93.21, 450; 435/7.2, 69.1, 172.3, 320.1; 514/44; 935/54, 55, 62, 71
SEARCH-FLD: 514/44; 435/320.1, 240.2, 6, 7.1, 69.1, 172.3, 69.5T, 7.2; 935/62, 52, 55, 56, 57, 32, 54, 66, 70, 71, 33, 34, 72, 65; 424/93.1, 93.2T, 130.1, 450; 536/23T
REF-CITED:

FOREIGN PATENT DOCUMENTS
WO 95/00178 1/1995 World Intellectual Property Organization

OTHER PUBLICATIONS
Blackman et al., Life Sci., 57(19):1717-1735, 1995.
Donnelly et al., Ann. N.Y. Acad. Sci., 772:40-46, 1995.
Liu, Ann. N.Y. Acad. Sci., 772(DNA Vaccines):15-21, 1995.
Miethke et al., Int. Arch. Allergy Immunol., 106:3-7, 1995.
Miethke et al., Immunobiol., 189:270-284, 1993.
Liu et al., 1997, Nature Biotechnology, 15:167-173.
ART-UNIT: 189
PRIM-EXMR: Jasemine C. Chambers

ASST-EXMR: Karen M[redacted] Hauda
LEGAL-REP: Sherida[redacted]oss P.C.

ABSTRACT:
The present invention provides a nucleic acid-based therapeutic composition to treat an animal with disease by controlling the activity of effector cells, including T cells, macrophages, monocytes and/or natural killer cells, in the animal. The present invention also relates to methods of **gene therapy** involving different modes of administration of a therapeutic composition to treat animals with different types of diseases. Also included in the present invention are recombinant molecules for use in a therapeutic composition and recombinant cells useful as a tumor vaccine. Therapeutic compositions of the present invention include superantigen-encoding nucleic acid molecules, either in the presence or absence of a cytokine-encoding nucleic acid molecule, depending upon the disease being treated.
52 Claims, 10 Drawing Figures

US PAT NO: 5,670,488 [IMAGE AVAILABLE] L1: 5 of 8
DATE ISSUED: Sep. 23, 1997
TITLE: **Adenovirus** vector for **gene therapy**
INVENTOR: Richard J. Gregory, Carlsbad, CA
Donna Armentano, Watertown, MA
Larry A. Couture, Framingham, MA
Alan E. Smith, Wellesley, MA
ASSIGNEE: Genzyme Corporation, Framingham, MA (U.S. corp.)
APPL-NO: 08/136,742
DATE FILED: Oct. 13, 1993
REL-US-DATA: Continuation-in-part of Ser. No. 985,478, Dec. 3, 1992, abandoned.
INT-CL: [6] A61K 48/00; C12N 15/00
US-CL-ISSUED: 514/44; 424/93.2; 435/320.1; 935/62
US-CL-CURRENT: 514/44; 424/93.2; 435/320.1; 935/62
SEARCH-FLD: 435/320.1; 514/44; 424/93.2; 935/62
REF-CITED:

U.S. PATENT DOCUMENTS

4,920,209	4/1990	Davis

FOREIGN PATENT DOCUMENTS

0 185 573	6/1986	European Patent Office
0 446 017	9/1990	European Patent Office
WO 91/02796	8/1990	World Intellectual Property Organization
WO 93/12240	12/1992	World Intellectual Property Organization
WO 93/12756	12/1992	World Intellectual Property Organization
WO 91/10734	12/1992	World Intellectual Property Organization
93 19191	9/1993	World Intellectual Property Organization

OTHER PUBLICATIONS

Zabner, J. et al. (1993) "Adenovirus-Mediated Gene Transfer Transiently Corrects the Chloride Transport Defect in Nasal Epithelia of Patients with Cystic Fibrosis" Cell 75:207-216.

Rosenfeld, M.A. et al. (1992) "In Vivo Transfer of the Human Cystic Fibrosis Transmembrane Conductance Regulator Gene to the Airway Epithelium" Cell 68: 143-155.

Sassone-Corsi, P. et al. (1983) "Far upstream sequences are required for efficient transcription from the adenovirus-2 E1A transcription unit" Nucleic Acid Research 11:8735-8745.

Yoshimura, K. et al. (1993) "Adenovirus-mediated Augmentation of Cell Transfection with Unmodified Plasmid Vectors" J. Biol. Chem.

268(4):2300-2303.
Engelhardt, J.F. et a 1993) "Direct Gene Transfer of [redacted]man CFTR into Human Bronchial Epithelia of Xenografts with E1-deleted Adenovirus" Nat. Gen. 4:27-34.
Flotte, T.R. et al. (1993) "Expression of the Cystic Fibrosis Transmembrane Conductance Regulator from a Novel Adeno-associated Virus Promoter" J. Biol. Chem. 268(5):3781-3790.
Johnson, L.G. et al. (1992) "Efficiency of Gene Transfer for Restoration of Normal Airway Epithelial Function in Cystic Fibrosis" Nat. Gen. 2:21-25.
Welsh, M.J. and Smith, A.E. (1993) "Molecular Mechanisms of CFTR Chloride Channel Dysfunction in Cystic Fibrosis" Cell 73:1251-1254.
Hyde, S.C. et al. (1993) "Correction of the Ion Transport Defect in Cystic Fibrosis Transgenic Mice by Gene Therapy" Nature 362:250-255.
Smith, A.E. (1992) "Emerging Therapies for Cystic Fibrosis" Section V-Topics in Biology in Ann. Rep. Med. Chem. 27:235-243.
Yoshimura, K. et al. (1992) "Expression of the Human Cystic Fibrosis Transmembrane Conductance Regulator Gene in the Mouse Lung after in Vivo Intratracheal Plasmid-Mediated Gene Transfer" Nucleic Acids Res. 20:(12):3233-3240.
Rosenfeld, M.A. et al. (1991) "Adenovirus-Mediated Transfer of a Recombinant .alpha.-1-Antitrypsin Gene to the Lung Epithelium in Vivo" Science 252:431-434.
Rosenfeld, M.A. et al. (1991) "In Vivo Transfer of the Human Cystic Fibrosis Gene to the Respiratory Epithelium" Clin. Res. 39(2):311A.
Anderson, M.P. et al. (1991) "Generation of cAMP-Activated Chloride Currents by Expression of CFTR" Science 251:679-682.
Kartner, N. et al. (1991) "Expression of the Cystic Fibrosis Gene in Non-Epithelial Invertebrate Cells Produces a Regulated Anion Conductance" Cell 64:681-691.
Anderson, M.P. et al. (1991) "Demonstration That CFTR Is a Chloride Channel by Alteration of Its Anion Selectivity" Science 253:202-205.
Tabcharani, J.A. et al. (1991) "Phosphorylation-Regulated Cl-Channel in CHO Cells Stabley Expressing the Cystic Fibrosis Gene" Nature 352:628-631.
Rich, D.P. et al. (1991) "Effect of Deleting the R Domain on CFTR-Generated Chloride Channels" Science 253:205-207.
Berger, H.A. et al. (1991) "Identification and Regulation of the Cystic Fibrosis Transmembrane Conductance Regulator-Generated Chloride Channel" J. Clin. Invest. 88:1422-1431.
Drumm, M.L. et al. (1990) "Correction of the Cystic Fibrosis Defect In Vitro By Retrovirus-Mediated Gene Transfer" Cell 1227-1233.
Gregory, R.J. et al. (1990) "Expression and Characterization of the Cystic Fibrosis Transmembrane Conductance Regulator" Nature 347:382-386.
Rich, D.P. et al. (1990) "Expression of the Cystic Fibrosis Transmembrane Conductance Regulator Corrects Defective Chloride Channel Regulation in Cystic Fibrosis Airway Epithelial Cells" Nature 347:358-363.
Huang, M.T.F. et al. (1990) "Intervening Sequences Increase Efficiency of RNA 3'Processing and Accumulation of Cytoplasmic RNA" Nucleic Acids Res. 18(4):937-947.
Riordan, J.R. et al. (1989) "Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA" Science 245:1066-1073.
Rommens, J.H. et al. (1989) "Identification of the Cystic Fibrosis Gene: Chromosome Walking and Jumping" Science 245: 1059-1065.
Kerem, B.S. et al. (1989) "Identification of the Cystic Fibrosis Gene: Genetic Analysis" Science 245:1073-1080.
Berker (1988) Biotechniques 6, 616-627.
ART-UNIT: 189
PRIM-EXMR: Deborah Crouch
LEGAL-REP: Brumbaugh, Graves Donohue & Raymond

ABSTRACT:
Gene Therapy vectors, which are especially useful for cystic

fibrosis, and methods for using the vectors are disclosed.
19 Claims, 67 Drawing Figures

=> d 5,clms

US PAT NO: 5,670,488 [IMAGE AVAILABLE] L1: 5 of 8

CLAIMS:

CLMS(1)

We claim:

1. An adenoviral vector comprising an **adenovirus** genome from which one or more of the E4 open reading frames has been deleted, but retaining sufficient E4 sequences to promote virus replication in vitro, and additionally comprising a DNA sequence of interest operably linked to expression control sequences and inserted into said adenoviral genome.

CLMS(2)

2. The vector of claim 1 wherein a PGK promoter is operably linked to the DNA sequence of interest.

CLMS(3)

3. The vector of claim 1 from which the Ela and Elb regions of the **adenovirus** genome have been deleted.

CLMS(4)

4. The vector of claim 1 from which the E3 region of the **adenovirus** genome has been deleted.

CLMS(5)

5. The adenoviral vector of claim 1 in which open reading frame 6 of the E4 region is retained in the **adenovirus** genome.

CLMS(6)

6. The adenoviral vector of claim 1 in which open reading frame 3 of the E4 region is retained in the **adenovirus** genome.

CLMS(7)

7. The adenoviral vector of claim 1 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(8)

8. The adenoviral vector of claim 2 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(9)

9. The adenoviral vector of claim 3 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(10)

10. The adenoviral vector of claim 3 wherein the DNA sequence is inserted into the deleted Ela and Elb regions of the adenoviral genome.

CLMS(11)

11. The adenoviral vector of claim 5 wherein the DNA sequence encodes cystic fibrosis transmembrane regulator protein.

CLMS(12)

12. The adenoviral vector of claim 6 wherein a cytomegalovirus promoter is operably linked to the DNA sequence of interest.

CLMS(13)

13. A method for providing cystic fibrosis transmembrane conductance regulator protein to airway epithelial cells of a cystic fibrosis patient comprising administering directly to airway epithelial cells of the patient an adenoviral vector, said vector comprising an **adenovirus** genome from which one or more E4 open reading frames has been deleted, but retaining sufficient E4 sequences to promote virus replication in vitro, and additionally comprising a DNA sequence encoding cystic fibrosis transmembrane regulator protein operably linked to expression control sequences and inserted into the E1 region said adenoviral genome, under conditions whereby the DNA sequence encoding cystic fibrosis transmembrane regulator protein is expressed and a functional chloride ion channel is produced in the airway epithelial cells of the patient.

CLMS(14)

14. The method of claim 13 wherein open reading frame 6 of the E4 region of the **adenovirus** genome is retained in the vector.

CLMS(15)

15. The method of claim 13 wherein the expression control sequences operably linked to the DNA sequence comprise the PGK promoter.

CLMS(16)

16. The method of claim 13 in which the Ela and Elb regions of the **adenovirus** genome of the vector have been deleted.

CLMS(17)

17. The method of claim 13 in which the E3 region of the **adenovirus** genome of the vector has been deleted.

CLMS(18)

18. The method of claim 13 wherein open reading frame 3 of the E4 region of the **adenovirus** genome is retained in the vector.

CLMS(19)

19. The method of claim 18 wherein the expression control sequences operably linked to the DNA sequence comprise a cytomegalovirus promoter.

=> d fro,1-3

US PAT NO: 5,780,300 [IMAGE AVAILABLE] L1: 1 of 8
DATE ISSUED: Jul. 14, 1998
TITLE: Manipulation of non-terminally differentiated cells using the notch pathway
INVENTOR: Spyridon Artavanis-Tsakonas, Hamden, CT
Mark Edward Fortini, New Haven, CT

Kenji M[redacted]suno, New Haven, CT
ASSIGNEE: Yale U[redacted]ersity, New Haven, CT (U.S. co
APPL-NO: 08/537,210
DATE FILED: Sep. 29, 1995
INT-CL: [6] C12N 5/08; C12N 5/02; C12N 5/06
US-CL-ISSUED: 435/377, 325, 366, 372, 375
US-CL-CURRENT: 435/377, 325, 366, 372, 375
SEARCH-FLD: 435/6, 69.1, 325, 366, 372, 377, 375
REF-CITED:

U.S. PATENT DOCUMENTS

5,226,914	7/1993	Caplan et al.	623/16
5,580,738	12/1996	Laborda	435/6

FOREIGN PATENT DOCUMENTS

92/19734	11/1992	World Intellectual Property Organization
92/22584	12/1992	World Intellectual Property Organization
93/12141	6/1993	World Intellectual Property Organization
94/07474	4/1994	World Intellectual Property Organization
94/07522	4/1994	World Intellectual Property Organization
94/08037	4/1994	World Intellectual Property Organization
94/13701	6/1994	World Intellectual Property Organization
95/19779	7/1995	World Intellectual Property Organization

OTHER PUBLICATIONS

Ahmad et al., 1995, "Involvement of Notch-1in mammalian retinal neurogenesis: Association of Notch-1activity with both immature and terminally differentiated cells", Mech. Dev. 53:73-85.

Artavanis-Tsakonas et al., 1995, "Notchsignaling", Science 268:225-232.

Austin et al., 1995, "Vertebrate retinal ganglion cells are selected from competent progenitors by the action of Notch"Development 121:3637-3650.

Axelrod et al., 1996, "Interaction between Wingless and Notch signaling pathways mediated by Dishevelled", Science 271:1826-1832.

Bettenhausen et al., 1995, "Transient and restricted expression during mouse embryogenesis of DII1, a murine gene closely related to Drosophila Delta", Development 121:2407-2418.

Bierkamp et al., 1993, "A zebrafish homologue of the Drosophila neurogene and its pattern of transcription during early embryo genesis", Mech Dev. 43:87-100.

Brou et al., 1994, "Inhibition of the DNA-binding activity of Drosophila Suppressor of Hairless and of its human homolog, KBF-2/RBP-J.kappa., by direct protein-protein interaction with Drosophila Hairless", Genes Dev. 8:2491-2503.

Cagan and Ready, 1089, "Notch is required for successive cell decisions in the developing Drosophila retina", Genes Dev. 3:1099-1112.

Chenn and McConnell, 1995, "Cleavage orientation and the asymmetric inheritance of Notch 1 immunoreactivity in mammalian neurogenesis", Cell. vol. 82:631-641.

Chitnis et al., 1993, "Primary neurogenesis in Xenopus embryos regulated by a homologue of the Drosophila neurogenic gene Delta ", Nature 375:761-766.

Coffman et al., 1993, "Expression of an exracellular deletion of Xotch diverts cell fate in Xenopus embryos", Cell 73:659-679.

Corbin et al., 1991, "A role for the Drosophila neurogenic genes in mesoderm differentiation", Cell 67:311-323.

Cummings and Cronmiller, 1994, "The daughterless gene functions together with Notch and Delta in the control of ovarian follicle development in Drosophila ", Development 120:381-394.

Delidakis et al., 1991, "Two genetically and molecularly distinct

functions involved in early neurogenesis reside within the enhancer of split locus of Drosophila melanogaster ", Genetics 1[illegible]803-823.
Dorsky et al., 1995, "Xotch inhibits cell differentiation in the Xenopus retina", Neuron 14:487-496.
Ellison et al., 1991, "Tan-1 , the human homolog of the Drosophila Notch gene, is broken by chromosomal translocations in T lymphoblastic neoplasms", Cell 66:649-661.
Fehon et al., "Molecular interactions between the protein products of the neurogenic loci Notch and Delta , two EGF-homologous genes in Drosophila ", Cell 61:523-534.
Fehon et al., 1991, "Complex cellular and subcellular regulation of Notch expression during embryonic and imaginal development of Drosophila : Implications for Notch function", J. Cell. Biol. 113:657-669.
Fleming et al., 1990, "The gene Serrate encodes a putative EGF-like transmembrane protein essential for proper ectodermal development in Drosophila melanogaster", Genes and Development 1:2188-2201.
Fortini et al., 1993, "An activated Notch receptor blocks cell-fate commitment in the developing Drosophila eye", Nature 365:555-557.
Fortini et al., 1993, "Notch: neurogenesis is only part of the picture", Cell 75:1245-1247.
Fortini et al., 1994, "The suppressor of hairless protein participates in Notch receptor signaling", Cell 79:273-282.
Fortini et al., 1992, "Signalling by the sevenless protein tyrosine kinase is mimicked by Ras 1 activation", Nature 355:559-561.
Franco del Amo et al., 1992, "Expression pattern of Motch, a mouse homolog of Drosophila Notch , suggests an important role in early postimplanlation mouse development", Development 115:737-744.
Giniger et al., 1993, "Specifying the path of the intersegmental nerve of the Drosophila embryo: a role for Delta and Notch", Development 117:431-440.
Goldspiel et al., 1993, "Human gene therapy"Clin. Pharm. 12:488-505.
Goshima et al., 1991, "the osteogenic potential of culture-expanded rat marrow mesenchymal cells assayed in vivo in calcium phosphate ceramic bolcks", Clin. Orthop. 262:298-311.
Greenwald and Rubin, 1992, "Making a difference: the role of cell-cell interactions in establishing separate identities for equivalent cells", Cell 68:271-281.
Greenwald, 1994, "Structure/function studies of lin -12/Notch proteins ", Curr. Opin. Genet. Dev. 4: 556-562.
Hartenstein et al., 1992, "The function of the neurogenic genes during epithelial development in the Drosophila embryo", Development, 116:1203-1220.
Hartenstein and Prosakony, 1990, "A dual function of the Notch gene in Drosophila sensillum development", Dev. Biol. 142:13-30.
Henrique et al., 1995, "Expression of a Delta homologue in prospective neurons in the chick", Nature 375:787-790.
Hing et al., 1994, "Modulation of wingless signaling by Notch in Drosophila ", Mech. Dev. 47:261-268.
Horvitz et al., 1991, "Multiple intercellular signalling systems control the development of the Caenorhabditis elegans vulva", Nature 351:535-541.
Jan et al., 1993, "Functional gene cassettes in developmant", Proc. Natl. Acad. Sci. USA 90:8305-8307.
Johansen et al., 1989, "The Notch gene product is a glycoprotein expressed on the cell surface of both epidermal and neuronal precursor cells during Drosophila development", J. Cell. Biol. 109:2427-2440.
Kidd et al., 1989, "Structure and distribution of the Notch protein in the development Drosophila ", Genes Dev. 3:1113-1129.
Kidd et al., 1986, "Sequence of the Notch locus of Drosophila melanogaster : Relationship of the encoded protein to mammalian clotting and growth factors", Mol. Cell. Biol. 6:3094-3108.
Knust et al., 1992, "Seven genes of the Enhancer of split complex of Drosophila melanogaster encode helix-loop-helix proteins"Genetics 132:505-518.
Kopan et al., 1993, "Mouse Notch : expression in hair follicles

correlates with cell fate determination", J. Cell. Biol. 121:631-641.
Kopan et al., 1994, "[redacted] intracellular domain of mouse [redacted]ch : a constitutively activated repressor of myogenesis directed at the basic helix-loop-helix region of MyoD", Development 120:2385-2396.
Kopczynski et al., "Delta, a Drosophila neurogenic gene, is transcriptionally complex and encodes a protein related to blood coagulation factors and epidermal growth factor of vertebrates", Genes and Development 2:1723-1735.
Lardelli et al., 1993, "MotchA and MotchB --two mouse Notch homologues are expressed in a wide variety of tissues", Exp. Cell Res. 204:364-372.
Lardelli et al., 1994, "The novel Notch homologue mouse Notch3 lacks specific epidermal growth factor-repeats and is expressed in proliferating neuroepithelium", Mech Dev. 46:123-136.
Larsson et al., 1994, "The human Notch 1,2, and 3 genes are located at chromosome positions 9q34, 1p13-p11, and 19p13.2-p13.1 in regions of neoplasia-associated translocation", Genomics 24:253-258.
Le Douarin et al., 1975, "Cholinergic differentiation of presumptive adrenergic neuroblasts in interspecific chimeras after heterotropic transplantations", Proc. Natl. Acad. USA 72:728-732.
Leff, 1995, "NIH proposes to grant ImClone license to tumor-targeting epidermal GF gene", BioWorld Today 6:2.
Lieber et al., 1993, "Antineurogenic phenotypes induced by truncated Notch proteins indictate a role in signal transduction and may point to a novel function for Notch in nuuclei", Genes and Development 7:1949-1965.
Lindsell et al., 1995, "Jagged: A mamalian ligand that activates Notch1 "Cell 80:909-917.
Lindvall et al., 1990, "Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease", Science 247:574-577.
Liu et al., 1996, "Epithelial expression and chromosomal location of human TLE genes: implications for Notch signaling and neoplasia", Genomics 31:58-64.
Lyman et al., 1993, "Further evidence for function of the Drosophila Notch protein as a transmembrane receptor", Proc. Natl. Acad. Sci. USA 90:10395-10399.
Markopoulo and Artavanis-Tsakonas, 1989, "The expression of the neorogenic locus Notch during the postembryonic development of Drosophila melanogaster and its relationship to mitotic activity", J. Neurogenetics 6:11-26.
Matsuno et al., 1995, "Deltex acts as a positive regulator of Notch signaling through interactions with the Notch ankyrin repeats", Development 121:2633-2644.
Morgan et al., 1993, "Human gene therapy", Annu. Rev. Biochem. 62:191-217.
Mulligan, 1993, "The basic science of gene therapy", Science 260:926-932.
Nusse and Varmus, 1992, "Wnt genes", Cell 69:1073-1087.
Rakic et al., 1982, "Early development events: cell lineages, acquisition of neuronal positions, and areal and laminar development", Neuroscience Res. Prog. Bull. 20:439-451.
Reaume et al., 1992 "Expression analysis of a Notch homologue in the mouse embryo", Dev. Biol. 154:377-387.
Roehl and Kimble, 1993, "Control of cell fate in C. elegans by a GLP-1 peptide consisting primarily of ankyrin repeats", Nature 364:632-635.
Ruohola et al., 1991, "Role of neurogenic genes in establishment of follicle and cell fate and oocyte polarity during oogenesis in Drosophila", Cell 66:433-449.
Schweisguth and Posakony, 1994, "Antagonistic activities of Suppressor of Hairless and Hairless control alternative cell fates in the Drosophila adult epidermis"Development 120:1433-1441.
Smoller et al., 1990, "The Drosophila neurogenic locus mastermindencodes a nuclear protein unusually rich in amino acid homopolymers", Genes Dev. 4:1688-1700.
Sternberg et al., 1993, "Falling off the knife edge", Curr. Bio. 3:763-765.

Stifani et al., 1992, "Human homologs of a Drosophila Enhancer of split gene product define a novel family of nuclear protein" Nature Genet. 2:119-127.
Struhl et al., 1993, "Intrinsic activity of the Lin-12 and Notch intracellular domains in vivo", Cell 74:331.
Struhl and Basler, 1993, "Organizing activity of wingless protein in Drosophila", Cell 72:527-540.
Sun and Artavanis-Tsakonas, 1996, "The intracellular deletions of Delta and Serrate define dominant negative forms of the Drosophila Notch ligands", Development 122:2465-2474.
Swiatek et al., 1994, "Notch1 is essential for the postimplantation development in mice", Genes Dev. 8:707-719.
Weinmaster et al., 1992, "Notch2 ; a second mammalian Notch gene", Development 116:931-941.
Weinmaster et al., 1991, "A homolog of Drosophila Notch expressed during mammalian development", Development 113:199-205.
Wharton et al., 1985, "Nucleotide sequence from the neurogenic locus Notch implies a gene product that shares homology with proteins containing EGF-like repeats", Cell 43:567-581.
Wu et al., 1991, "Delivery sysems for gene therapy", Biotherapy 3:87-95.
Xu et al., 1992, "The involvement of the Notch locus in Drosophila oogenesis", Development 115:913-922.
Zagouras et al., 1995, "Alterations in Notch signaling in neoplastic lesions of the human cervix", Proc. Natl. Acad. Sci. USA 92:6414-6418.
Orkin et al. Report & Recommendations of The Panel to Asses the NIH Investment in Research on Gene Therapy 1995.
ART-UNIT: 185
PRIM-EXMR: Nancy Degen
LEGAL-REP: Pennie & Edmonds LLP

ABSTRACT:
The present invention is directed to methods for the expansion of non-terminally differentiated cells ("precursor cells") using agonists of Notch function, by inhibiting the differentiation of the cells without inhibiting proliferation (mitotic activity) such that an expanded population of non-terminally differentiated cells is obtained. The cells are preferably stem or progenitor cells. These expanded cells can be used in cell replacement therapy to provide desired cell populations and help in the regeneration of diseased and/or injured tissues. The expanded cell populations can also be made recombinant and used for **gene therapy**, or can be used to supply functions associated with a particular precursor cell or its progeny cell.
40 Claims, 16 Drawing Figures

US PAT NO: 5,741,772 [IMAGE AVAILABLE] L1: 2 of 8
DATE ISSUED: Apr. 21, 1998
TITLE: Neurotrophic factor NNT-1
INVENTOR: Ming-shi Chang, Newbury Park, CA
ASSIGNEE: Amgen Inc., Thousand Oaks, CA (U.S. corp.)
APPL-NO: 08/792,019
DATE FILED: Feb. 3, 1997
INT-CL: [6] A01N 37/18; A61K 38/00
US-CL-ISSUED: 514/2; 530/300, 350
US-CL-CURRENT: 514/2; 530/300, 350
SEARCH-FLD: 530/300, 350; 514/2
REF-CITED:

OTHER PUBLICATIONS

Humpel, et al., Science, 269:552-554 [1995].
Isackson, Current Opinions in Neurobiology 5:50-357 [1995].
MacDonald and Hendrikson, Cell, 73:421-424 [1993].
Nedivi et al (Nature, 363:718-722 [1993].
Nedivi et al., Proc. Natl. Acad. Sci USA, 93:2048-2053 [1996].
ART-UNIT: 188

PRIM-EXMR: Marian Knode
ASST-EXMR: Heathe Bakalyar
LEGAL-REP: Robert R. Cook, Ron K. Levy, Steven Odre

ABSTRACT:
Disclosed are nucleic acids encoding novel neurotrophic factors, designated NNT-1. Also disclosed are amino acid sequences for NNT-1 polypeptides, methods for preparing NNT-1 polypeptides, and other related aspects.

6 Claims, 14 Drawing Figures

US PAT NO: 5,707,618 [IMAGE AVAILABLE] L1: 3 of 8
DATE ISSUED: Jan. 13, 1998
TITLE: **Adenovirus** vectors for **gene therapy**
INVENTOR: Donna Armentano, Belmont, MA
Helen Romanczuk, Westboro, MA
Samuel Charles Wadsworth, Shrewsbury, MA
ASSIGNEE: Genzyme Corporation, Framingham, MA (U.S. corp.)
APPL-NO: 08/409,874
DATE FILED: Mar. 24, 1995
INT-CL: [6] A61K 48/00; C12N 15/00; C12N 5/00
US-CL-ISSUED: 424/93.21, 93.2; 435/172.3, 240.1, 240.2, 320.1; 514/44
US-CL-CURRENT: 424/93.21, 93.2; 435/172.3, 320.1; 514/44
SEARCH-FLD: 514/44, 2; 435/235.1, 172.1, 172.3, 240.1, 240.2, 91.1; 424/93.2, 93.21
REF-CITED:

FOREIGN PATENT DOCUMENTS

WO9412649	12/1993	World Intellectual Property Organization
9424297	10/1994	World Intellectual Property Organization
9502697	1/1995	World Intellectual Property Organization
WO9511984	5/1995	World Intellectual Property Organization

OTHER PUBLICATIONS

Zabner et al., Gene Therapy 3:458-465, 1996.
Armentano et al., Human Gene Therapy 6:1343-1353, 1995.
Krougliak et al., Human Gene Therapy 6:1575-1586, 1995.
Welsh et al., Human Gene Therapy 6:205-218, 1995.
Wadsworth et al., J. Cell Biochem. Supp. 21A, Abstract No. c6-450, 1995.
Setoguchi et al., Blood 84:2946-2953, 1994.
Engelhardt et al., Human Gene Therapy 5:1217-1229, 1994.
Armentano et al., J. Cell Biochem. Supp. 18A, Abstract no. DZ 102, 1994.
Wilkinson et al., Nucleic Acids Res. 20:2233-2239, 1992.
Rosenfeld et al., Cell 68:143-155, 1992.
Jolly, D., Cancer Gene Therapy 1:51-64, 1994.
Marshall, Science: 269:1050-1055, 1995.
Neve, Trends in Neuroscience 16(7):251-253, 1993.
Berkner, BioTechniques 6(7):616-629, 1988.
NIH, "Report and Recommendations . . . ", Dec. 7, 1995, pp. 1-40.
Vincent et al., Nature Genetics 5:130-134, 1993.
Descamps et al., Human Gene Therapy 5:979-985, 1994.
Stratford-Perricaudet et al., Human Gene Therapy 1:241-256, 1990.
Mitani et al., Human Gene Therapy 5:941-948, 1994.
Haddada et al., Human Gene Therapy 4:703-711, 1993.
Jaffe et al., Nature Genetics 1:372-378, 1992.
Zabner, J. et al., Nature Genetics 6:75-83, 1994.
Rich, D. et al.,Human Gene Therapy 4:461-476, 1993.
Zabner, J. et al., Cell 75:207-216, 1993.
Crystal, R.G. et al., Nature Genetics 8:42-51, 1994.
Bridge, E. et al., J. Virol. 63:631-638, 1989.
Huang, M. et al., J. Virol. 63:2605-2615, 1989.

Klessig, D. et al., Mo[redacted] Cell. Biol. 4:1354-1362, 1984.
Weinberg, D. et al., P[redacted]. Natl. Acad. Sci. USA 80:5383[redacted]86, 1983.
ART-UNIT: 184
PRIM-EXMR: Jacqueline M. Stone
ASST-EXMR: Andrew Milne
LEGAL-REP: Brumbaugh, Graves, Donohue & Raymond

ABSTRACT:
The present invention relates to novel **adenovirus** vectors for use in **gene therapy** which are designed to prevent the generation of replication-competent **adenovirus** (RCA) during in vitro propagation and clinical use. The invention also provides methods for the production of the novel virus vectors. These vectors maximize safety for clinical applications in which **adenovirus** vectors are used to transfer genes into recipient cells for **gene therapy**.
8 Claims, 3 Drawing Figures

=> s adenovir?(5A)vector? and gene therapy

```
          2971 ADENOVIR?
         67874 VECTOR?
           572 ADENOVIR?(5A)VECTOR?
         18155 GENE
         37863 THERAPY
          1230 GENE THERAPY
                 (GENE(W)THERAPY)
L2         258 ADENOVIR?(5A)VECTOR? AND GENE THERAPY
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=> s l2 and thymidine kinase?

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          7525 THYMIDINE
          7859 KINASE?
          1475 THYMIDINE KINASE?
                 (THYMIDINE(W)KINASE?)
L3          97 L2 AND THYMIDINE KINASE?
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=> s l3 and prodrug?

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          2808 PRODRUG?
L4           8 L3 AND PRODRUG?
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=> d l4,1-8,cit

1. 5,772,993, Jun. 30, 1998, Osteocalcin promoter-based toxic **gene therapy** for the treatment of calcified tumors and tissues; Leland W. K. Chung, et al., 424/93.6, 9.2; 435/71.2, 320.1; 514/44 [IMAGE AVAILABLE]

2. 5,731,182, Mar. 24, 1998, Non-mammalian DNA virus to express an exogenous gene in a mammalian cell; Frederick M. Boyce, 435/183, 69.1, 70.1, 320.1 [IMAGE AVAILABLE]

3. 5,716,832, Feb. 10, 1998, Packaging cells; Jack R. Barber, et al., 435/172.3, 325 [IMAGE AVAILABLE]

4. 5,698,446, Dec. 16, 1997, Methods and compositions for inhibiting production of replication competent virus; Wolfgang M. Klump, et al., 435/350, 320.1, 366 [IMAGE AVAILABLE]

5. 5,691,177, Nov. 25, 1997, Recombinant retroviruses expressing a protein that converts a pro-drug into a cytotoxic agent; Harry E. Guber, et al., 435/172.3, 69.1, 372 [IMAGE AVAILABLE]

6. 5,631,236, May 20, 1997, **Gene therapy** for solid tumors, using

a DNA sequence encodin[redacted]SV-Tk or VZV-Tk; Savio L. C. W[redacted] et al., 514/44; 424/93.6; 435/[redacted].1 [IMAGE AVAILABLE]

7. 5,591,624, Jan. 7, 1997, Retroviral packaging cell lines; Jack R. Barber, et al., 435/366, 172.3, 320.1, 369 [IMAGE AVAILABLE]

8. 5,352,595, Oct. 4, 1994, Myod regulatory region; Stephen J. Tapscott, et al., 435/172.3, 320.1, 325, 354, 357; 536/24.1 [IMAGE AVAILABLE]

=> d l4,6,fro

US PAT NO: 5,631,236 [IMAGE AVAILABLE] L4: 6 of 8
DATE ISSUED: May 20, 1997
TITLE: **Gene therapy** for solid tumors, using a DNA sequence encoding HSV-Tk or VZV-Tk
INVENTOR: Savio L. C. Woo, Houston, TX
Shu-Hsia Chen, Houston, TX
ASSIGNEE: Baylor College of Medicine, Houston, TX (U.S. corp.)
APPL-NO: 08/112,745
DATE FILED: Aug. 26, 1993
INT-CL: [6] A61K 48/00; A01N 63/00; C12N 5/00
US-CL-ISSUED: 514/44; 424/93.6; 435/320.1
US-CL-CURRENT: 514/44; 424/93.6; 435/320.1
SEARCH-FLD: 514/44
REF-CITED:

OTHER PUBLICATIONS

Stratford-Perricaudet, et al.; Evaluation of the Transfer and Expression in Mice of an Enzyme-Encoding Gene Using a Human Adenovirus Vector; Human Gene Therapy; 1:241-256 (1990).

O'Malley, et al.; Adenovirus-mediated Gene Therapy for Human Head and Neck Squamous Cell Cancer in a Nude Mouse Model; Cancer Research; 55:1080-1085 (1995).

Chen, et al.; Combination gene therapy for liver metastasis of colon carcinoma in vivo; Proc. Natl. Acad. Sci. USA; 92:2577-2581 (1955).

Bonnekoh, et al.; Inhibition of Melanoma Growth by Adenoviral-Mediated HSV Thymidine Kinase Gene Transfer In Vivo; J. Invest. Dermatol.; 104:313-317 (1995).

Chen, et al.; Gene therapy for brain tumors: Regression of experimental gliomas by adenovirus-mediated gene transfer in vivo; Proc. Natl. Acad. Sci. USA; 91:3054-3057 (1994).

Smythe, et al.; Successful Adenovirus-Mediated Gene Transfer in an In Vivo Model of Human Malignant Mesothelioma; Ann. Thorac. Surg.; 57:1395-401 (1994).

Perez-Cruet, et al.; Adenovirus-Mediated Gene Therapy of Experimental Gliomas; J. Neurosci. Res.; 39:506-511 (1994).

Caruso; et al.; Regression of established macroscopic liver metastases after in situ transduction of a suicide gene; Proc. Natl. Acad. Sci. USA; 90:7024-7028 (1993).

Gray, et al.; Antisense DNA Inhibition of Tumor Growth Induced by c-Ha-ras Oncogene in Nude Mice; Cancer Res. 53:577-80 (1993).

Fujiwara, et al.; Induction of Chemosensitivity in Human Lung Cancer Cells in Vivo by Adenovirus-mediated Transfer of the Wild-Type p53 Gene; Cancer Res. 54:2287-91 (1994).

Ezzeddine, et al.; Selective Killing of Glioma Cells in Culture and in Vivo by Retrovirus Transfer of the Herpes Simplex Virus Thymidine Kinase Gene; The New Biologist 6:608-14 (1991).

Hann, et al.; Antitumor Effect of Deferoxamine on Human Hepatocellular Carcinoma Growing in Athymic Nude Mice; Cancer 8:2051-56 (1992).

Pantazis, et al.; Camptothecin Derivatives Induce Regression of Human Ovarian Carcinomas Grown in Nude Mice and Distinguish Between Non-Tumorigenic and Tumoringenic Cells In Vitro; Int. J. Cancer 53:863-71 (1993).

Wakeling, et al.; A P t Specific Pure Antiestrogen with Clinical Potential; Cancer R 51:3867-73 (1991).
Pietras, et al.; Antibody to HER-2/neu receptor blocks DNA repair after cisplatin in human breast and ovarian cancer cells; Oncogene 9:1829-38 (1994).
Ogura; Implantation of Genetically Manipulated Fibroblasts into Mice as Antitumor .alpha.-Interferon Therapy; Cancer Res. 50:5102-06 (1990).
Gastl, et al.; Retroviral Vector-mediated Lymphokine Gene Transfer into Human Renal Cancer Cells; Cancer Res. 52:6229-36 (1992).
Shin (1979) Meth. Enzmol. LVIII, 370-379.
Rosenfeld et al (1991) Science 252, 431-434.
Culver et al (1992) Science 256, 1550-1552.
ART-UNIT: 184
PRIM-EXMR: Jacqueline M. Stone
ASST-EXMR: Deborah Crouch
LEGAL-REP: Fulbright & Jaworski LLP

ABSTRACT:
The present invention provides a novel method of treating localized solid tumors and papilloma in an individual. The method comprises introducing a recombinant **adenoviral vector** containing the herpes simplex virus-**thymidine kinase** gene. Subsequently, a **prodrug**, such as the drug ganciclovir, is administered to the individual. The methods of the present invention may be used to treat several different types of cancers and papillomas, including colon carcinoma, prostate cancer, breast cancer, lung cancer, melanoma, hepatoma, brain and head and neck cancer.
6 Claims, 16 Drawing Figures

=> d 1,fro

US PAT NO: 5,772,993 [IMAGE AVAILABLE] L4: 1 of 8
DATE ISSUED: Jun. 30, 1998
TITLE: Osteocalcin promoter-based toxic **gene therapy** for the treatment of calcified tumors and tissues
INVENTOR: Leland W. K. Chung, Lovingston, VA
Chinghai Kao, Charlottesville, VA
Robert A. Sikes, Charlottesville, VA
Song-Chu Ko, Charlottesville, VA
Jun Cheon, Sol, Republic of Korea
ASSIGNEE: The University of Virginia Patent Foundation, Charlottesville, VA (U.S. corp.)
APPL-NO: 08/785,088
DATE FILED: Jan. 21, 1997
INT-CL: [6] A61K 48/00; A01N 63/00; C12P 21/04; C12N 15/00
US-CL-ISSUED: 424/93.6; 514/44; 435/320.1, 71.2; 424/9.2
US-CL-CURRENT: 424/93.6, 9.2; 435/71.2, 320.1; 514/44
SEARCH-FLD: 424/9.2, 93.6; 514/44; 435/320.1, 71.2
REF-CITED:

OTHER PUBLICATIONS

Su et al Human Gene Therapy (1996) Mar. 1 7(4) 463-70.
Henderson et al WO 9701358 Jan. 16, 1997.
Ko et al Cancer Res Oct. 15, 1996, 56(20) pp. 4614-4619.
ART-UNIT: 186
PRIM-EXMR: Lila Feisee
ASST-EXMR: Geetha P. Bansal
LEGAL-REP: Oblon, Spivak, McClelland, Maier & Neustadt, P.C.

ABSTRACT:
A recombinant adenovirus Ad-OC-TK was constructed, with cell specific gene expression, which contains osteocalcin (OC) promoter that drives the expression of herpes simplex virus **thymidine kinase** (TK); the

addition of acyclovir (ACV), a pro-drug for the inhibition of cell proliferation, to Ad-OC-TK resulted in the induction of osteoblast-specific cell death in vitro. The Ad-OC-TK virus plus ACV treatment is highly selective in blocking the growth of both murine and human osteosarcoma cell lines in vitro and murine osteosarcoma in vivo.

6 Claims, 20 Drawing Figures

08/958570

attachment to Paper #4

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           16723  THYMIDINE KINASE?
      S1     728  ADENOVIRUS? AND THYMIDINE KINASE?
? s s1 and gene therapy?

             728  S1
           42313  GENE THERAPY?
      S2     337  S1 AND GENE THERAPY?
? s s2 and prodrug?

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           47211  PRODRUG?
      S3      60  S2 AND PRODRUG?
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      Display 4/3/1     (Item 1 from file: 154)
DIALOG(R)File 154:MEDLINE(R)
(c) format only 1998 Dialog Corporation. All rts. reserv.

09559188   98280347
    In vivo adenovirus-mediated prodrug gene therapy for
carcinoembryonic antigen-producing pancreatic cancer.
  Ohashi M; Kanai F; Tanaka T; Lan KH; Shiratori Y; Komatsu Y; Kawabe T;
Yoshida H; Hamada H; Omata M
  Second Department of Internal Medicine, Faculty of Medicine, University
of Tokyo.
  Jpn J Cancer Res (JAPAN)  Apr 1998,  89 (4) p457-62,  ISSN 0910-5050
Journal Code: HBA
  Languages: ENGLISH
  Document type: JOURNAL ARTICLE

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Display 4/3/2 (Item 2 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09550709 98276752
Severe hepatic dysfunction after **adenovirus**-mediated transfer of the herpes simplex virus thymidine kinase gene and ganciclovir administration.
van der Eb MM; Cramer SJ; Vergouwe Y; Schagen FH; van Krieken JH; van der Eb AJ; Rinkes IH; van de Velde CJ; Hoeben RC
Department of Surgery, Leiden University Medical Center, The Netherlands.
Gene Ther (ENGLAND) Apr 1998, 5 (4) p451-8, ISSN 0969-7128 Journal Code: CCE
Languages: ENGLISH
Document type: JOURNAL ARTICLE

- end of record -

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Display 4/3/3 (Item 3 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09468305 98196519
Adenoviral-mediated transfer of a heat-inducible double suicide gene into prostate carcinoma cells.
Blackburn RV; Galoforo SS; Corry PM; Lee YJ
Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, Michigan 48073-6769, USA.
Cancer Res (UNITED STATES) Apr 1 1998, 58 (7) p1358-62, ISSN 0008-5472 Journal Code: CNF
Contract/Grant No.: CA48000, CA, NCI; CA44550, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

- end of record -

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Display 4/3/4 (Item 4 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09420935 98133159
Characterization of the antitumor immune response generated by treatment of murine tumors with recombinant **adenoviruses** expressing HSVtk, IL-2, IL-6 or B7-1.
Felzmann T; Ramsey WJ; Blaese RM
Clinical Gene Therapy Branch, NHGRI, NIH, Bethesda, MD, USA.
Gene Ther (ENGLAND) Dec 1997, 4 (12) p1322-9, ISSN 0969-7128 Journal Code: CCE
Languages: ENGLISH
Document type: JOURNAL ARTICLE

- end of record -

?

Display 4/3/5 (Item 5 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09308508 97425065
Gene therapy vector: **adenovirus** vector]
Saito I
Laboratory of Molecular Genetics, University of Tokyo, Japan.

Tanpakushitsu Kakusan Koso (JAPAN) Jul 1997, 42 (10 Suppl) p1798-805, ISSN 0039-9450 Journal Code: Q7D
Languages: JAPANESE
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

- end of record -

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Display 4/3/6 (Item 6 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09290044 98010140
Retinoids augment the bystander effect in vitro and in vivo in herpes simplex virus thymidine kinase/ganciclovir-mediated gene therapy.
Park JY; Elshami AA; Amin K; Rizk N; Kaiser LR; Albelda SM
Department of Medicine, Kyunpook National University School of Medicine, Korea.
Gene Ther (ENGLAND) Sep 1997, 4 (9) p909-17, ISSN 0969-7128 Journal Code: CCE
Contract/Grant No.: PO1 66726
Languages: ENGLISH
Document type: JOURNAL ARTICLE

- end of record -

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Display 4/3/7 (Item 7 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09144104 97397467
The effect of promoter strength in adenoviral vectors containing herpes simplex virus thymidine kinase on cancer gene therapy in vitro and in vivo.
Elshami AA; Cook JW; Amin KM; Choi H; Park JY; Coonrod L; Sun J; Molnar-Kimber K; Wilson JM; Kaiser LR; Albelda SM
Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, USA.
Cancer Gene Ther (UNITED STATES) Jul-Aug 1997, 4 (4) p213-21, ISSN 0929-1903 Journal Code: CE3
Contract/Grant No.: PO1 66726
Languages: ENGLISH
Document type: JOURNAL ARTICLE

- end of record -

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Display 4/3/8 (Item 8 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

09108617 97372865
Adenoviral thymidine kinase **prodrug** gene therapy inhibits sarcoma growth in vivo.
Ross HM; Hirschowitz EA; Russi TJ; Crystal RG; Nawata S; Burt ME; Brennan MF; Lewis JJ
Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, USA.
J Surg Res (UNITED STATES) Jun 1997, 70 (1) p7-11, ISSN 0022-4804 Journal Code: K7B
Languages: ENGLISH
Document type: JOURNAL ARTICLE

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Display 4/3/9 (Item 9 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08940238 97189005
Adenovirus -mediated suicide gene therapy for experimental bladder cancer.
Sutton MA; Berkman SA; Chen SH; Block A; Dang TD; Kattan MW; Wheeler TM; Rowley DR; Woo SL; Lerner SP
Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030, USA.
Urology (UNITED STATES) Feb 1997, 49 (2) p173-80, ISSN 0090-4295 Journal Code: WSY
Languages: ENGLISH
Document type: JOURNAL ARTICLE

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Display 4/3/10 (Item 10 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08651357 96317698
[Gene therapy for cancer]
Sakamaki S; Niitsu Y
Fourth Department of Internal Medicine, Sapporo Medical University School of Medicine, Japan.
Hokkaido Igaku Zasshi (JAPAN) Jan 1996, 71 (1) p15-20, ISSN 0367-6102 Journal Code: GA9
Languages: JAPANESE Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL English Abstract

- end of record -
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Display 4/3/11 (Item 11 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08495108 96051281
Gene therapy for hepatocellular carcinoma: chemosensitivity conferred by **adenovirus**-mediated transfer of the HSV-1 thymidine kinase gene.
Wills KN; Huang WM; Harris MP; Machemer T; Maneval DC; Gregory RJ
CANJI, Inc., San Diego, California 92121, USA.
Cancer Gene Ther (UNITED STATES) Sep 1995, 2 (3) p191-7, ISSN 0929-1903 Journal Code: CE3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

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Display 4/3/12 (Item 12 from file: 154)
DIALOG(R)File 154:MEDLINE(R)

08030924 95024189
In vivo suppression of injury-induced vascular smooth muscle cell accumulation using **adenovirus**-mediated transfer of the herpes simplex virus thymidine kinase gene.
Guzman RJ; Hirschowitz EA; Brody SL; Crystal RG; Epstein SE; Finkel T
Cardiology Branch, National Heart, Lung, and Blood Institute, National

Institutes of Health, Bethesda, MD 20892.
Proc Natl Acad Sci U[redacted]A (UNITED STATES) Oct 25 19 91 (22) p10732-6
, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE

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Display 4/3/13 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

06374820 Genuine Article#: YN172 No. References: 26
Title: **Adenovirus**-mediated enzyme-**prodrug** therapy for cancer
Author(s): Kanai F (REPRINT) ; Hamada H; Shiratori Y; Omata M
Corporate Source: UNIV TOKYO,FAC MED, DEPT INTERNAL MED 2, BUNKYO KU, 7-3-1 HONGO/TOKYO 113//JAPAN/ (REPRINT); JAPANESE FDN CANC RES,CTR CANC CHEMOTHERAPY, DEPT MOL BIOTHERAPY RES, TOSHIMA KU/TOKYO 170//JAPAN/
Journal: CANCER JOURNAL, 1997, V10, N6 (NOV-DEC), P301-305
ISSN: 0765-7846 Publication date: 19971100
Publisher: ASSOC DEVELOPPEMENT COMMUNICATION CANCEROLOGIQUE, CANCER JOURNAL, 7 RUE GUY MOQUET, BP 8, 94801 VILLEJUIF, FRANCE
Language: English Document Type: REVIEW (ABSTRACT AVAILABLE)

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Display 4/3/14 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

06315655 Genuine Article#: YJ111 No. References: 41
Title: Suicide genes for gene therapy of cancer
Author(s): Finocchiaro G; Rosolen A
Corporate Source: NEUROL NATL INST CARLO BESTA,DEPT BIOCHEM & GENET/I-20133 MILAN//ITALY/; UNIV PADUA,DEPT PEDIAT/I-35100 PADUA//ITALY/
Journal: MINERVA BIOTECNOLOGICA, 1997, V9, N4 (DEC), P188-195
ISSN: 1120-4826 Publication date: 19971200
Publisher: EDIZIONI MINERVA MEDICA, CORSO BRAMANTE 83-85 INT JOURNALS DEPT., 10126 TURIN, ITALY
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

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Display 4/3/15 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

05630389 Genuine Article#: WM093 No. References: 36
Title: Possibilities of gene therapies for cancer
Author(s): Lashford LS (REPRINT)
Corporate Source: CHRISTIE HOSP NHS TRUST,ACAD UNIT PAEDIAT ONCOL, WILMSLOW RD/MANCHESTER M20 4BX/LANCS/ENGLAND/ (REPRINT)
Journal: ANNALS OF MEDICINE, 1997, V29, N1 (FEB), P1-4
ISSN: 0785-3890 Publication date: 19970200
Publisher: BLACKWELL SCIENCE LTD, OSNEY MEAD, OXFORD, OXON, ENGLAND OX2 0EL
Language: English Document Type: EDITORIAL MATERIAL (ABSTRACT AVAILABLE)

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Display 4/3/16 (Item 4 from file: 34)

DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

05567731 Genuine Article#: WG542 No. References: 48
Title: Gene-directed enzyme **prodrug** therapy (GDEPT): Choice of **prodrugs**
Author(s): Springer CJ (REPRINT) ; NiculescuDuvaz I
Corporate Source: INST CANC RES,CRC, CTR CANC THERAPEUT, 15 COTSWOLD RD/SUTTON SM2 5NG/SURREY/ENGLAND/ (REPRINT)
Journal: ADVANCED DRUG DELIVERY REVIEWS, 1996, V22, N3 (DEC 15), P351-364
ISSN: 0169-409X Publication date: 19961215
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: REVIEW (ABSTRACT AVAILABLE)

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Display 4/3/17 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

05429352 Genuine Article#: VY322 No. References: 308
Title: APPROACHES TO ENHANCE CANCER RADIOTHERAPY EMPLOYING GENE-TRANSFER METHODS
Author(s): BUCHSBAUM DJ; RABEN D; STACKHOUSE MA; KHAZAELI MB; ROGERS BE; ROSENFELD ME; LIU T; CURIEL DT
Corporate Source: UNIV ALABAMA,GENE THERAPY PROGRAM,1824 6TH AVE S/BIRMINGHAM//AL/35294; UNIV ALABAMA,GENE THERAPY PROGRAM/BIRMINGHAM//AL/35294; UNIV ALABAMA,DEPT RADIAT ONCOL/BIRMINGHAM//AL/00000; UNIV ALABAMA,DEPT MED/BIRMINGHAM//AL/35294
Journal: GENE THERAPY, 1996, V3, N12 (DEC), P1042-1068
ISSN: 0969-7128
Language: ENGLISH Document Type: REVIEW (Abstract Available)

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Display 4/3/18 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

05082471 Genuine Article#: TN767 No. References: 37
Title: EXPRESSION OF THE BACTERIAL NITROREDUCTASE ENZYME IN MAMMALIAN-CELLS RENDERS THEM SELECTIVELY SENSITIVE TO KILLING BY THE **PRODRUG** CB1954
Author(s): BRIDGEWATER JA; SPRINGER CJ; KNOX RJ; MINTON NP; MICHAEL NP; COLLINS MK
Corporate Source: CHESTER BEATTY LABS,CRC,CTR CELL & MOLEC BIOL,237 FULHAM RD/LONDON SW3 6JB//ENGLAND/; CHESTER BEATTY LABS,CRC,CTR CELL & MOLEC BIOL/LONDON SW3 6JB//ENGLAND/; INST CANC RES,CRC,CTR CANC THERAPEUT/SUTTON SM25NG/SURREY/ENGLAND/; CTR APPL MICROBIOL & RES,DIV RES,DEPT MOLEC MICROBIOL/SALISBURY SP4 0JG/WILTS/ENGLAND/
Journal: EUROPEAN JOURNAL OF CANCER, 1995, V031A, N13-1 (DEC), P2362-2370
ISSN: 0959-8049
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

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Display 4/3/19 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 1998 Inst for Sci Info. All rts. reserv.

04913455 Genuine Article#: UR302 No. References: 34
Title: GENE-THERAPY FOR MALIGNANT GLIOMAS USING REPLICATION INCOMPETENT

RETROVIRAL AND ADENOVIRAL VECTORS ENCODING THE CYTOCHROME-P450 2B1 GENE TOGETHER WITH CYCLOPHOSPHAMIDE
Author(s): MANOME Y; WEN PY; CHEN L; TANAKA T; DONG Y; YAMAZOE M; HIRSHOWITZ A; KUFE DW; FINE HA
Corporate Source: HARVARD UNIV,SCH MED,DANA FARBER CANC INST,DIV CANC PHARMACOL,DANA 1560,44 BINNEY ST/BOSTON//MA/02115; HARVARD UNIV,SCH MED,DANA FARBER CANC INST,DIV CANC PHARMACOL/BOSTON//MA/02115; HARVARD UNIV,BRIGHAM & WOMENS HOSP,SCH MED,DIV NEUROL/BOSTON//MA/02115
Journal: GENE THERAPY, 1996, V3, N6 (JUN), P513-520
ISSN: 0969-7128
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

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Display 4/3/20 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10586787 EMBASE No: 97365586
Relative efficiency of tumor cell killing in vitro by two enzyme-**prodrug** systems delivered by identical **adenovirus** vectors
Lockett L.J.; Molloy P.L.; Russell P.J.; Both G.W.
G.W. Both, Division of Molecular Science, CSIRO, P.O. Box 184, North Ryde, NSW 2113 Australia
Clinical Cancer Research (United States) , 1997, 3/11 (2075-2080)
CODEN: CCREF ISSN: 1078-0432
DOCUMENT TYPE: Journal Article
LANGUAGES: ENGLISH SUMMARY LANGUAGES: ENGLISH
NUMBER OF REFERENCES: 29

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Display 4/3/21 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

10087186 EMBASE No: 96280007
Use of von Willebrand factor promoter to transduce suicidal gene to human endothelial cells, HUVEC
Ozaki K.; Yoshida T.; Ide H.; Saito I.; Ikeda Y.; Sugimura T.; Terada M.
Genetics Division, Natl. Cancer Center Research Inst., 5-1-1 Tsukiji, Chuo-ku, Tokyo 104 Japan
Human Gene Therapy (USA) , 1996, 7/13 (1483-1490)
CODEN: HGTHE ISSN: 1043-0342
LANGUAGES: English SUMMARY LANGUAGES: English

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Display 4/3/22 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

9903003 EMBASE No: 96085188
Adenovirus-mediated **prodrug** gene therapy for carcinoembryonic antigen- producing human gastric carcinoma cells in vitro
Tanaka T.; Kanai F.; Okabe S.; Yoshida Y.; Wakimoto H.; Hamada H.; Shiratori Y.; Lan K.-H.; Ishitobi M.; Omata M.
Second Dept. of Internal Medicine, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113 Japan
Cancer Research (USA) , 1996, 56/6 (1341-1345)
CODEN: CNREA ISSN: 0008-5472
LANGUAGES: English SUMMARY LANGUAGES: English

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Display 4/3/23 (Item 1 from file: 76)
DIALOG(R)File 76:Life Sciences Collection

01958042 3798439
In vivo marking of spontaneous or vaccine-induced fibrosarcomas in the domestic house cat, using an adenoviral vector containing a bifunctional fusion protein, GAL-TEK
Marini, F.C.,III; Cannon, J.P.; Belmont, J.W.; Shillitoe, E.J.; Lapeyre, J. N.
Dep. Exp. Pathol., Univ. Texas M.D. Anderson Cancer Cent., Houston, TX 77054, USA
HUM. GENE THER. vol. 6, no. 9, pp. 1215-1223 (1995)
ISSN: 1043-0342
DOCUMENT TYPE: Journal article LANGUAGE: ENGLISH
SUBFILE: Human Genome Abstracts; Agricultural and Environmental Biotechnology Abstracts

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Display 4/3/24 (Item 1 from file: 94)
DIALOG(R)File 94:JICST-EPlus

04325664 JICST ACCESSION NUMBER: 97A0928215 FILE SEGMENT: JICST-E
New Device for Cancer Gene Therapy. Gene therapy by tumor-specific **prodrug** activation.
KANAI FUMIHIKO (1); OMATA MASAO (1); HAMADA HIROFUMI (2)
(1) Univ. of Tokyo, Fac. of Med.; (2) Cancer Chemother. Center, Jpn. Found. for Cancer Res.
Ketsueki, Shuyoka(Hematology & Oncology), 1997, VOL.35,NO.4, PAGE.347-352, FIG.1, TBL.2, REF.20
JOURNAL NUMBER: Z0127BBF ISSN NO: 0915-8529
UNIVERSAL DECIMAL CLASSIFICATION: 616-08
LANGUAGE: Japanese COUNTRY OF PUBLICATION: Japan
DOCUMENT TYPE: Journal
ARTICLE TYPE: Commentary
MEDIA TYPE: Printed Publication

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Display 4/3/25 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

13162102 PASCAL No.: 97-0423639
Preclinical testing of recombinant adenoviral herpes simplex virus-thymidine kinase gene therapy for central nervous system malignancies. Commentaries
VINCENT A J P E; ESANDI M DEL C; AVEZAAT C J J; VECHT C; SMITT P S; VAN BEKKUM D W; VALERIO D; HOOGERBRUGGE P M; BOUT A; BLACK K L comment; RUTKA J T comment; ZLOKOVIC B V comment
Department of Neurosurgery, University Hospital Rotterdam, Netherlands; Section Group Gene Therapy, Department of Medical Biochemistry, University of Leiden, Netherlands; Department of Neuro-oncology, Daniel den Hoed Clinic Rotterdam, Netherlands; IntroGene BV, Rijswijk, Netherlands; Department of Pediatrics, University Hospital Rotterdam, Rotterdam, Netherlands
Journal: Neurosurgery, 1997, 41 (2) 442-452

Language: English

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Display 4/3/25 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

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Display 4/3/26 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

12913073 PASCAL No.: 97-0181263
Adenovirus-mediated herpes simplex virus thymidine kinase gene and ganciclovir therapy leads to systemic activity against spontaneous and induced metastasis in an orthotopic mouse model of prostate cancer
HALL S J; MUTCHNIK S E; CHEN S H; WOO S L C; THOMPSON T C
Matsunaga-Conte Prostate Cancer Research Center and Scott Department of Urology, Baylor College of Medicine, Houston, TX 77030, United States; Department of Cell Biology, Baylor College of Medicine, Houston, TX 77030, United States; Howard Hughes Medical Institute, Baylor College of Medicine, Houston, TX 77030, United States; Urology Research Laboratory, VA Medical Center, Baylor College of Medicine, Houston, TX 77030, United States; Department of Radiotherapy, Baylor College of Medicine, Houston, TX 77030, United States
Journal: International journal of cancer, 1997, 70 (2) 183-187
Language: English

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Display 4/3/26 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

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Display 4/3/27 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

11545878 PASCAL No.: 94-0428054
Use of recombinant **adenovirus** to transfer the Herpes simplex virus thymidine kinase (HSVtk) gene to thoracic neoplasms : an effective in vitro drug sensitization system
ROY SMYTHE W; HWANG H C; AMIN K M; ECK S L; DAVIDSON B L; WILSON J M; KAISER L R; ALBELDA S M
Univ. Pennsylvania thoracic oncology res. lab., dep. surgery, thoracic surgery sect., Philadelphia PA, USA
Journal: Cancer research : (Baltimore), 1994, 54 (8) 2055-2059
Language: English

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Display 4/3/27 (Item 3 from file: 144)
DIALOG(R)File 144:Pascal

11545878 PASCAL No.: 94-0428054
Use of recombinant **adenovirus** to transfer the Herpes simplex virus thymidine kinase (HSVtk) gene to thoracic neoplasms : an effective in vitro drug sensitization system
ROY SMYTHE W; HWANG H C; AMIN K M; ECK S L; DAVIDSON B L; WILSON J M; KAISER L R; ALBELDA S M
Univ. Pennsylvania thoracic oncology res. lab., dep. surgery, thoracic surgery sect., Philadelphia PA, USA
Journal: Cancer research : (Baltimore), 1994, 54 (8) 2055-2059
Language: English

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